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(54) Title: A PROCESS FOR PREPARING LONG CHAIN SATURATED OR UNSATURATED OXYGENATED COMPOUNDS

(57) Abstract: A process for preparing long chain saturated or unsaturated oxygenated compounds. The process for the preparation of long-chain saturated or unsaturated oxygenated compounds having from 20 to 36 carbon atoms, selected from the group consisting of polycosanoic acids, their alkyl esters, polycosanols and corresponding compounds having an unsaturated hydrocarbon chain comprises the operation of reacting, in accordance with the Wittig or Peterson olefination reaction, a phosphorus ylide $RP(Ar)_3$, wherein R is a saturated or unsaturated hydrocarbon chain containing one or more ethylenic and/or acetylenic unsaturations and Ar is aryl, or the corresponding α-silylcarbanion, respectively, with an n-alkanoic acid, formylated in the terminal position, or with its corresponding alkyl ester.

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A process for preparing long chain saturated or unsaturated oxygenated compounds

The present invention relates to a synthesis process for the preparation of saturated or unsaturated long-chain oxygenated compounds, and particularly of polycosanols, polycosanoic acids, their alkyl esters and corresponding unsaturated compounds.

The term "polycosanols" is intended to indicate linear long-chain primary aliphatic alcohols having from 20 to 36 carbon atoms; of particular interest within the scope of the invention are the compounds having from 26 to 30 carbon atoms.

Polycosanols are known as compounds having pharmacological activity, particularly in the treatment of hypercholesterolaemia; their use as anti-inflammatory and antithrombotic agents is also known, as is their activity in improving sexual activity.

Typically, mixtures of polycosanols are obtained by extraction processes from natural waxes, such as, for example, bees-wax, sugar cane wax and rice wax.

The processes of extraction with a solvent from natural substances result in the obtainment of complex mixtures of polycosanols from which it is possible to obtain a single compound of interest only after expensive purification operations.

For example, EP-A-0 619 802 describes a mixture of polyco-

sanols which is obtained from sugar cane and which contains, as principal components, 1-octacosanol and 1-triacontanol together with smaller amounts of 1-tetracosanol, 1-heptacosanol, 1-dotriacontanol and 1-tetratriacontanol.

Processes for the preparation of polycosanols by reduction of the corresponding n-alkanoic acids or polycosanoic acids obtained by synthesis are also known.

US Patent 4 294 770 describes a process for the synthesis of long-chain n-alkanoic acids, which can be used as intermediates for the preparation of the corresponding polycosanols, by reaction of trihalomethane with normal-α-olefins having from 25 to 35 carbon atoms in the presence of a radical initiator and by subsequent alkaline hydrolysis of the trihaloalkane so obtained. A disadvantage associated with that process resides in the fact that normal-α-olefins having from 25 to 35 carbon atoms are not commercially available in the pure state and therefore the process does not permit the production of polycosanoic acids and corresponding polycosanols that are substantially pure, except at the cost of expensive purification operations.

An object of the present invention is to provide an improved process which permits the production of polycosanoic acids, their esters and/or polycosanols, and also the production of corresponding unsaturated compounds with a limited number of synthesis steps starting from commercially available and inexpensive reagents.

Another object of the invention is to provide a process which permits the production of individual polycosanols and polycosanoic acids and corresponding mono- or poly-unsaturated compounds of high purity.

In view of those objects, the invention relates to a process as defined in the claims which follow.

The key step of the synthesis according to the invention is a Wittig olefination reaction (cf. Merck Index, 12a ed., ONR-99 and bibliographical references mentioned therein) in which a phosphorus ylide $RP(Ar)_3$, wherein Ar is aryl(phenyl) and R is a saturated or unsaturated hydrocarbon chain, particularly a phosphorus ylide of a linear alkane, alkene, diene, triene or alkyne, is reacted with an n-alkanoic acid, formylated in the terminal position, or with its corresponding alkyl ester (preferably lower alkyl having from 1 to 4 carbon atoms) to give the addition product constituted by the acid or alkyl ester with intermediate ethylenic unsaturation, having the desired chain length.

Alternatively, it is possible to operate in accordance with the Peterson olefination reaction (Merck Index, 12^{th} ed., ONR-69) which uses, instead of the above-mentioned phosphorus ylide, the α-silylcarbanion of a linear alkane; however, the Peterson reaction is less preferred owing to the greater difficulty of forming the α-silylcarbanions.

The process according to the invention can be used for the preparation of polycosanols and polycosanoic acids, their es-

ters and corresponding mono- or poly-unsaturated compounds generally having from 20 to 36 carbon atoms and preferably having from 26 to 30 carbon atoms; the compounds of greatest interest being octacosanol and octacosanoic acid and their C_{27} homologues.

In general, for the preparation of the desired compounds of formula $CH_3-(CH_2)_p-X$, wherein:
p is an integer, preferably from 22 to 34, or more preferably from 24 to 28, and
X is $-CH_2OH$, or $-COOR_1$ wherein R_1 denotes hydrogen or C_1-C_4 lower alkyl,
or of corresponding mono- or poly-unsaturated compounds having a hydrocarbon chain, it is possible to vary the chain length of both reagents.

For example, in the Wittig reaction - for the preparation of saturated or mono-unsaturated compounds - a phosphorus ylide of formula:

$$CH_3-(CH_2)_m-P(Ar)_3$$

is used
in which:
m is an integer from 8 to 22 carbon atoms, and
Ar is aryl, preferably phenyl,
which is reacted with a compound of formula

$$O=CH-(CH_2)_n-COOR_1,$$

wherein:
n is an integer from 2 to 12 and preferably from 6 to 12, and
R_1 has the meaning defined above,
and wherein:
n + m + 1 is equal to p.

Similar considerations apply in relation to the Peterson reaction.

Analogously, for the preparation of poly-unsaturated compounds, a phosphorus ylide $R_3P(Ar)_3$ is used wherein R_3 is an unsaturated hydrocarbon chain, for example, including from 1 to 4 ethylenic and/or acetylenic unsaturations.

However, in the preferred embodiment, the saturated or unsaturated compounds and particularly the polycosanols and the polycosanoic acids having the desired chain length are prepared using 10-oxo-decanoic acid or its alkyl ester, varying the hydrocarbon chain length of the phosphorus ylide.

In this preferred embodiment, the starting reagent used is 10-undecenoic acid which is an inexpensive commercially available product in a highly purified form (purity 99%).

In this embodiment, the 10-undecenoic acid is preferably protected by an esterification reaction and the ester of the undecylenic acid so obtained is then subjected to oxidation of the terminal unsaturation to aldehyde.

It is, however, possible to proceed directly with oxidation without previous esterification.

For example, the operation is effected in accordance with the following operative stages:

1. Esterification of undecylenic acid with alcohol (methanol)

Method a)

The reaction is catalysed with acid (preferably *p*-toluene-sulphonic acid) and heating under reflux is effected in a solvent (preferably toluene) in the presence of methanol; the water is removed using a Dean Stark or Markusson distilling apparatus.

Method b)

The reaction is carried out with magnetic agitation at ambient temperature in methanol in the presence of acetyl chloride as the catalyst, with reaction times of the order of 7 hours.

1.1 Oxidative clearage of the terminal alkene to aldehyde

Method a)

The oxidation is effected with catalytic amounts of osmium tetroxide (for example, 0.01 molar equivalents, 0.2 M solution in toluene) and sodium periodate in an ether/water solution with agitation at ambient temperature with reaction times of approximately 3 hours.

Method b)

With catalytic osmium tetroxide (for example, 0.005 molar equivalents, 0.2 M solution in toluene) and sodium periodate in an acetone/water solution with magnetic agitation at ambient temperature and in the presence of N-methylmorpholine N-oxide as the co-oxidant, with reaction times of the order of approximately 90 minutes.

Method c)

With potassium permanganate, previously mixed with acid alu-

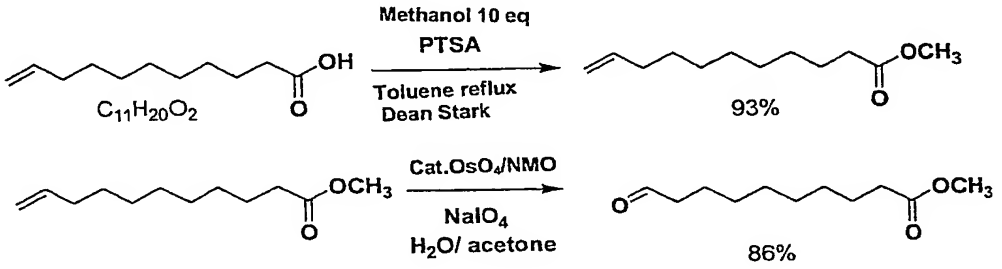
mina, preferably in the ratio 1:2.5 and an equal amount by weight of water with magnetic agitation in dichloromethane; approximately 10% of the corresponding carboxylic acid is obtained together with the aldehyde.

Method d)

With potassium permanganate and sodium periodate in water with vigorous agitation at ambient temperature.

Bearing in mind the cost of osmium tetroxide (OsO_4) or the equivalent potassium osmate ($K_2OsO_4.2H_2O$), method b) mentioned above, which permits the use of small catalytic amounts of osmium in the presence of a cooxidant, such as N-methylmorpholine N-oxide, is clearly preferred.

The following scheme summarises the reaction conditions indicated above, according to the preferred embodiment which uses 10-undecylenic acid.



NMO: N-methylmorpholine N-oxide

The n-alkane phosphorus ylide used in the Wittig reaction is prepared by reacting the corresponding halogen derivative (where halogen is preferably bromine or chlorine) with triphenylphosphine, preferably in a high-boiling solvent (toluene)

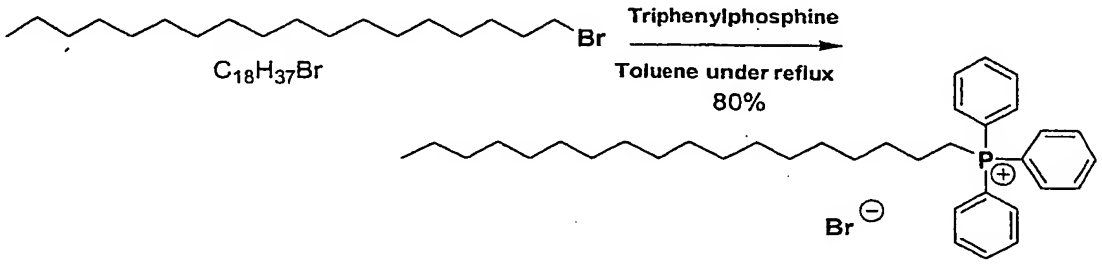
while heating under reflux; at the end of the reaction, the solution is concentrated and the phosphonium salt is precipitated, preferably with ether.

For the preparation of octacosanol and octacosanoic acid, 1-bromooctadecane is a reagent which is widely commercially available, with a high degree of purity (at least 96%), and inexpensive.

The following scheme illustrates the preparation of the phosphonium salt of 1-bromooctadecane.

2. Preparation of the phosphonium salt of 1-bromooctadecane

Heating is effected under reflux with triphenylphosphine in toluene for 24 hours; the solution is concentrated and the phosphonium salt is precipitated with ether.



3. Wittig reaction

The Wittig reaction can be carried out using n-alkanoic acid, formylated in the terminal position, or the corresponding alkyl ester, preferably methyl ester, operating in accordance with the following reaction conditions.

A) Reaction carried out on the alkyl ester: the phosphonium

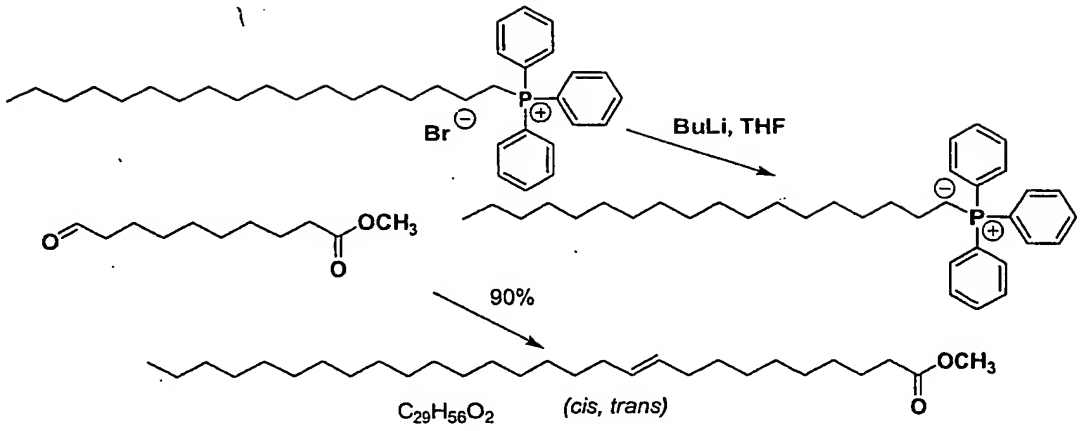
salt (preferably bromide) of n-alkane is converted into phosphorus ylide by reaction with a strong base (preferably butyl lithium) in an ethereal solvent, preferably tetrahydrofuran; the conversion is characterized by the colour change from yellow to intense orange. The aldehyde solution, preferably in tetrahydrofuran, prepared in point 1 above, is then added dropwise to give the cis-trans mixture of C_1-C_4 alkyl polycosenoate.

B) On the acid:

1. The phosphorus ylide is prepared by reacting the n-alkane phosphonium salt (bromide) with a strong base; the preferred conditions provide for the use of at least two molar equivalents of butyl lithium in THF in order to salify the carboxylic function present in the formyl acid, the solution of which (preferably in tetrahydrofuran) is subsequently added dropwise to give the cis-trans mixture of the desired polycosenoic acid.

2. First of all the sodium salt of n-alkanoic acid, which is formylated in the terminal position using sodium hydride in tetrahydrofuran, is prepared; the solvent is evaporated and then the procedure is as in point A indicated above.

The Wittig reaction, relating to the preparation of cis-trans methyl octacosenoate using methyl 10-oxo-decanoate, is illustrated in the following scheme.



The (C-10) mono-unsaturated C_1-C_4 alkyl esters (alcoholic component) having from 20 to 36 carbon atoms (acid component) constitute novel synthetic intermediates, forming the subject-matter of the present invention.

4. The above-mentioned mono-unsaturated alkyl ester or the corresponding acid is then subjected to catalytic hydrogenation of the double bond, for example, operating with palladium on carbon, to obtain the corresponding saturated compound. The catalytic hydrogenation conditions are known *per se* and do not require further explanation.

When the Wittig reaction is carried out using the above-mentioned alkyl ester, the desired polycosanol can be obtained by reduction of the saturated ester (after catalytic hydrogenation of the olefin), for example, using lithium aluminium hydride in tetrahydrofuran, for 3 hours at ambient temperature with agitation.

Alternatively, the saturated ester obtained by catalytic hydrogenation is converted into polycosanoic acid by alkaline hydrolysis.

By way of example, the hydrolysis of the ester can be carried out in accordance with the following methods:

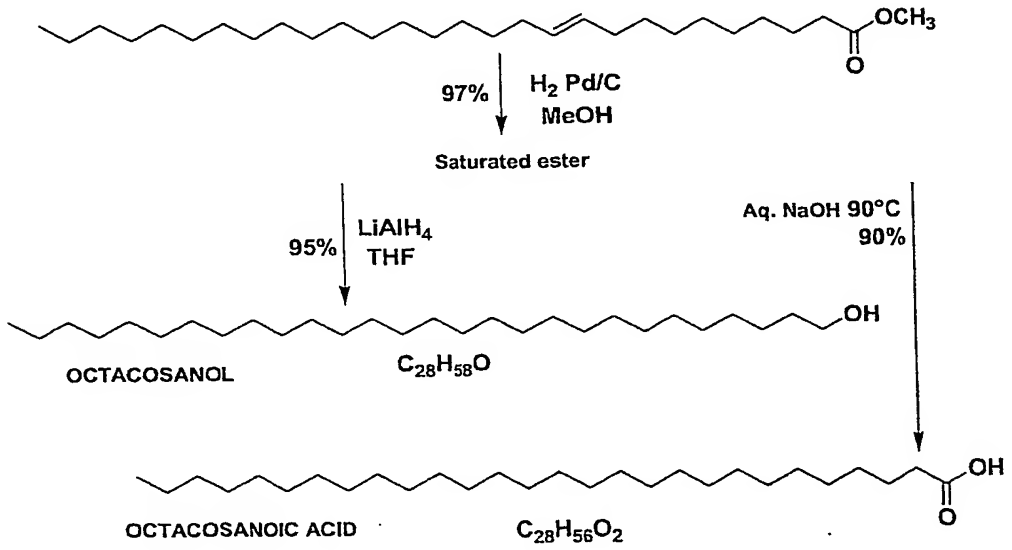
a) hydrolysis of the ester with aqueous NaOH, heating at 90°C for 2 hours;

b) hydrolysis of the ester to acid with caustic potash in hydroalcoholic solution;

c) hydrolysis of the ester with LiOH in hydroalcoholic solution.

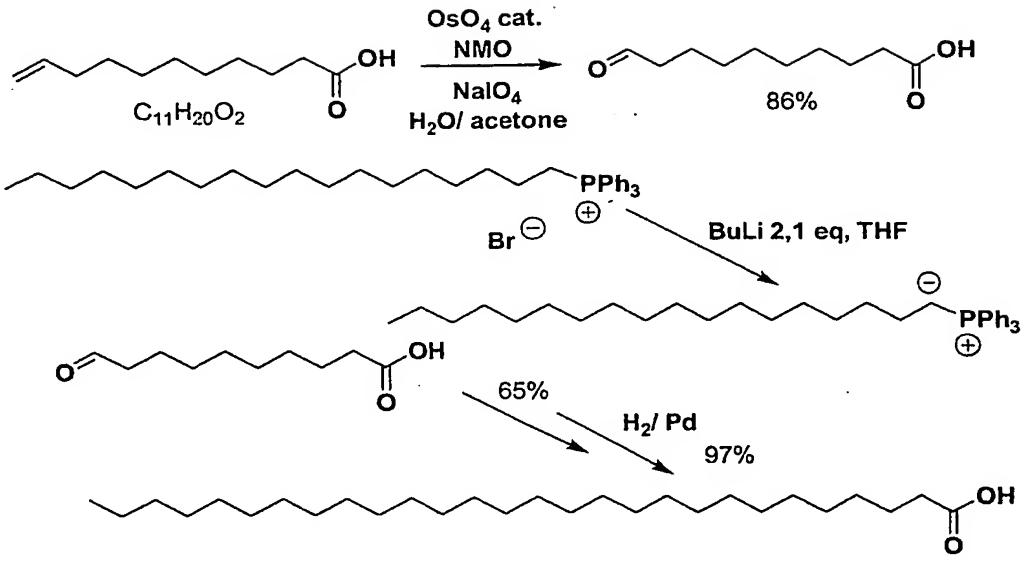
As indicated above, the catalytic hydrogenation reaction is preferably carried out directly on the unsaturated alkyl ester in view of the greater solubility of the ester in a hydroalcoholic solvent.

The following scheme illustrates the reaction stages for the conversion of cis-trans methyl octacosenoate into octacosanol and octacosanoic acid.



The scheme for the synthesis of octacosanoic acid, without protecting the undecylenic acid, is illustrated in the fol-

lowing scheme.



NMO: N-methylmorpholine N-oxide

It will be appreciated that, in this reaction scheme, the n-alkanoic acids obtained directly can, if desired, be converted into corresponding alcohols by known reduction reactions.

On the other hand, the polycosanoic acids and particularly octacosanoic acid and the corresponding C_1-C_4 alkylene esters are compounds which are useful per se in view of their powerful activity in the treatment of hypercholesterolaemia and also their powerful antithrombotic and anti-inflammatory activity.

HPLC analysis, NMR, mass spectrometry (EI-MS and CI-MS) and gas chromatographic analysis of the products obtained confirmed the absolute purity of the samples.

In the reaction schemes given in the present description, the reaction conditions are to be understood as being by way of non-limiting example.

The preparation of octacosanoic acid and octacosanol is described further in the specific working Examples which follow.

Example 1 - Methyl ester of undecylenic acid

In a two-necked 100 ml flask, 7 ml of methanol and a spatula tip of *p*-toluenesulphonic acid are added to 15 g of undecylenic acid (81.4 mmol) dissolved in 35 ml of anhydrous toluene. The whole is heated under reflux for 8 hours with a Dean Stark or Markusson distilling apparatus separating the water of esterification. All of the glassware used has been dried beforehand in an oven at 120°C. The progress of the reaction is monitored by TLC (silica gel plates), eluant hexane/EtOAc 7:3. R_f ester = 0.64.

Work-up: the product is diluted with EtOAc, washed twice with a mixture of $NaHCO_3/H_2O$ 1:1, then with H_2O and saturated NaCl solution and dried over Na_2SO_4. 15 g (73.0 mmol) are obtained, (yield 93%). Any traces of starting acid can be removed by filtration over a bed of alumina.

Example 2 - methyl 10-oxo-decanoate

In a 500 ml flask, 2.5 ml of a 0.2 M solution of OsO_4 in toluene (0.005 eq; 1.03 mmol) and 24.13 g of *N*-methylmorpholine-*N*-oxide (1 eq) are added to 40.86 g of the methyl ester of undecylenic acid (0.206 mmol) dissolved in 100 ml of a 1:1 H_2O/acetone mixture. The whole is left under agitation

for 15 minutes at 0°C in ice. 79.31 g of $NaIO_4$ (1.8 eq; 0.37 mmol) are then added in small portions over a period of 40 minutes at ambient temperature. The reaction is followed by TLC (silica gel plates), eluant hexane/ EtOAc 7:3 R_f product = 0.5.

Work-up: the product is filtered on a funnel having a sintered porous baffle, diluted with EtOAc, washed with a saturated NaCl solution and dried over Na_2SO_4. The product is then purified on a chromatographic column of silica gel (CC) eluant hexane/EtOAc 9:1. 35.3 g of methyl 10-oxo-decanoate (176.6 mmol) are obtained. (Yield 86%).

Example 3 - Phosphonium salt of 1-bromooctadecane

In a 250 ml flask, 1 eq of triphenylphosphine (24.6 g) is added to 30 g of 1-bromooctadecane (0.09 mmol) dissolved in 80 ml of anhydrous toluene. The whole is heated under reflux in a heating jacket for 24 hours. It is then cooled in a bath of water and ice for approximately 10 minutes and then approximately 15 ml of diethyl ether are added. The phosphonium salt precipitates in abundance, is filtered on a funnel having a sintered porous baffle and is washed with approximately 50 ml of ether. 41 g of a pearly pink solid (71.2 mmol) are obtained. (Yield 80%).

Example 4 - Methyl ester of 10-octacosenoic acid

In a 1 ℓ two-necked flask, 32 g of phosphonium salt (56.0 mmol) are dissolved in 350 ml of anhydrous THF with magnetic agitation in a nitrogen atmosphere. All of the glassware used has been dried beforehand in an oven at 120°C. 1.05 eq of a solution of BuLi (1.6 M in hexane) (34 ml) are slowly added

dropwise; the reaction mixture turns progressively orange-red, which indicates the formation of the ylide. After approximately 20 minutes, 5 ml of a solution containing 10.08 g of methyl 10-oxo-decanoate (0.9 eq; 50.4 mmol) are slowly added dropwise; during the addition of the aldehyde, the colour of the solution becomes yellow-orange. The whole is left under magnetic agitation overnight. The reaction is monitored by TLC (silica gel plates), eluant hexane/EtOAc 9:1. R_f product = 0.65.

Work-up: the product is diluted with a 0.1N HCl solution and extracted with EtOAc; washing is effected with a saturated NaCl solution and the whole is dried over Na_2SO_4. 19.2 g of product (45.1 mmol) are obtained. (Yield 90%).

Example 5 - 10-octacosenoic acid

In a 100 ml flask, 5 g of the methyl ester of 10-octacosenoic acid (11.8 mmol) in admixture with an aqueous 3.5N NaOH solution (30 ml) are heated at 90°C for 3 hours. The reaction is monitored by TLC (silica gel plates), eluant hexane/EtOAc 8:2. R_f product = 0.31.

Work-up: the mixture is acidified with 1N HCl and extracted with CH_2Cl_2. The organic phase is washed with saturated NaCl solution and dried over Na_2SO_4. 4.48 g of 10-octacosenoic acid (10.6 mmol) are obtained. (Yield 90%).

Example 6 - Octacosanoic acid

4.48 g of 10-octacosenoic acid (10.6 mmol) dissolved in 30 ml of methanol are subjected to catalytic hydrogenation with palladium on carbon in a Parr hydrogenator at 25 atm. and at

approximately 45°C (6 hours). The whole is filtered over a bed of celite in a funnel having a sintered porous baffle and the solvent is evaporated under vacuum. TLC (silica gel plates) eluant hexane/EtOAc 8:2. R_f product = 0.30. 4.32 g (10.2 mmol) are obtained. (Yield 96%).

Example 7 - 10-octacosenol

There are introduced into a 100 ml flask 8 g of the methyl ester of 10-octacosenoic acid (19.0 mmol) dissolved in 30 ml of anhydrous THF, and 1.44 g of $LiAlH_4$ (2 eq) subdivided into two portions (the second after 2 hours). The whole is left under magnetic agitation in an N_2 atmosphere for 4 hours. The reaction is monitored by TLC (silica gel plates), eluant hexane/EtOAc 9:1. R_f product = 0.58.

Work-up: the mixture is acidified with 0.2N H_2SO_4 and extracted with CH_2Cl_2. The organic phase is washed with a saturated NaCl solution and dried over Na_2SO_4. 7.36 g of product (18.0 mmol) are obtained. (Yield 95%).

Example 8 - Octacosanol

7.36 g of octacosenol (18 mmol) dissolved in 30 ml of methanol are subjected to catalytic hydrogenation with palladium on carbon in a Parr hydrogenator at 25 atm. (6 hours). The whole is filtered over a bed of celite in a funnel having a sintered porous baffle and the solvent is evaporated under vacuum. 7.14 g (17.5 mmol) are obtained. (Yield 97%). TLC (silica gel plates) eluant hexane/EtOAc 9:1. R_f product = 0.57.

Similarly to the Examples given above, it is possible to pre-

pare the corresponding polyunsaturated compounds using - instead of 1-bromo-octadecane - corresponding unsaturated compounds, for example, cis-1-bromo-9-octadecene, 1-bromo-9,12-octadecadiene or 1-bromo-9,12,15-octadecatriene.

The unsaturated compounds have, in general, a better activity compared with the corresponding polycosanols and polycosanoic acids and can therefore be used advantageously in the pharmaceutical, cosmetic and nutritional field (particularly for dietetic nutrition integrators), in which the polycosanols and polycosanoic acids are typically used.

These compounds have a high degree of antioxidant activity and a high degree of activity in the capture of free radicals, which enables them to be used both in cosmetic and nutritional compositions as antioxidants, in order to prevent the oxidative deterioration of those compositions, and in cosmetic and dermatological compositions for topical use, for the prevention and treatment of skin damage caused by free radicals, such as, in particular, for the treatment and prevention of inflammatory and ageing effects of the skin.

The unsaturated compounds are also characterized by a higher hypocholesterolaemic and/or hypolipidaemic activity in addition to a favourable effect on the lipoprotein picture (increase in HDL) compared with the corresponding polycosanols; they are therefore suitable for use in the preparation of medicaments and pharmaceutical compositions that can be used for the treatment and prevention of pathologies related to hypercholesterolaemia and hyperlipidaemia, such as, for example, cardiovascular diseases of the ischaemic or atheroscle-

rotic type and peripheral vascular diseases, and also for the prevention and cure of pathologies associated with an increased ability of blood platelets to aggregate and with a reduced oxygenation and nourishing of tissue, such as, for example, peripheral neuropathies and, in particular, diabetic peripheral neuropathy.

CLAIMS

1. A process for the preparation of linear or optionally branched long-chain oxygenated compounds having a saturated or unsaturated main chain with from 20 to 36 carbon atoms, and having a terminal functional group selected from an alcoholic ($-CH_2OH$), carboxylic (-COOH) or ester group, in particular compounds selected from the group consisting of polycosanoic acids, their alkyl esters, polycosanols and corresponding compounds having an unsaturated hydrocarbon chain, characterized in that it comprises the operation of reacting, in accordance with the Wittig or Peterson olefination reaction, a phosphorus ylide $RP(Ar)_3$, wherein R is a saturated or unsaturated hydrocarbon chain containing one or more ethylenic and/or acetylenic unsaturations and Ar is aryl, or the corresponding α-silylcarbanion, respectively, with an n-alkanoic acid, formylated in the terminal position, or with its corresponding alkyl ester.

2. A process according to claim 1, for the preparation of a polycosanoic acid, an ester thereof, or a polycosanol of formula (I):

$$CH_3-(CH_2)_p-X,$$

wherein

X is $-COOR_1$ or $-CH_2OH$, where R_1 is hydrogen or C_1-C_4 alkyl,

p is an integer from 22 to 34,

or a corresponding compound having a mono-unsaturated hydrocarbon chain,

characterized in that it comprises the operation of:

a) reacting a compound of formula (II):

$$O = CH-(CH_2)_n-COOR_1,$$

wherein

R_1 is hydrogen or C_1-C_4 alkyl and

n is an integer from 2 to 12, preferably from 6 to 12,

with a phosphorus ylide of formula (III):

$$CH_3-(CH_2)_m-P(Ar)_3,$$

wherein

m is an integer from 8 to 22,

Ar is aryl

in order to obtain the coupling product constituted by polycosenoic acid or alkyl ester.

3. A process according to claim 2, characterized in that it also comprises:

b) the catalytic hydrogenation of the polycosenoic acid or alkyl ester on the double bond to obtain the corresponding saturated compound.

4. A process according to claim 3, characterized in that a compound of formula (II) is used, wherein R_1 is alkyl having from 1 to 4 carbon atoms and wherein the C_1-C_4 alkyl ester of polycosanoic acid, obtained from stage b), is converted into the corresponding polycosanol by reduction of the ester to alcohol in the presence of lithium aluminium hydride.

5. A process according to claim 3, characterized in that a compound of formula (II) is used, wherein R_1 is alkyl having from 1 to 4 carbon atoms and wherein the C_1-C_4 alkyl ester of polycosanoic acid, obtained from stage b), is converted into the corresponding polycosanoic acid by basic hydrolysis.

6. A process according to claim 3, characterized in that a

compound of formula (II) is used, wherein R_1 is hydrogen, to obtain, as the reaction product of stage b), a polycosanoic acid.

7. A process according to any one of claims 2 to 6, characterized in that the compound of formula (II) is obtained by oxidative clearage to aldehyde of the corresponding terminal alkene.

8. A process according to claim 7, characterized in that the oxidative clearage is effected using sodium periodate, in the presence of catalytic amounts of osmium tetroxide.

9. A process according to claim 7, characterized in that the oxidative clearage is effected in the presence of catalytic amounts of osmium with sodium periodate and N-methylmorpholine N-oxide as co-oxidant.

10. A process according to claim 7, characterized in that the oxidative clearage is effected using alkali metal permanganate in the presence of acid alumina.

11. A process according to claim 7, characterized in that the oxidative clearage is effected with alkali metal permanganate and sodium periodate.

12. A process according to any one of claims 2 to 11, characterized in that the compound of formula (II) is 10-oxo-decanoic acid or C_1-C_4 alkyl 10-oxo-decanoate.

13. A process according to any one of claims 2 to 12, charac-

terized in that the phosphorus ylide is prepared by reacting the corresponding n-alkane, halogen-substituted in the terminal position, with triphenylphosphine to obtain the phosphonium salt of the haloalkane and converting the phosphonium salt into phosphorus ylide in the presence of an organometal compound.

14. A process according to claim 13, wherein the organometal compound is butyl lithium.

15. A process according to claim 13 or 14, wherein the phosphorus ylide of n-alkane is the phosphorus ylide of octadecane.

16. A process according to claim 1, for the preparation of unsaturated compounds of formula:

$$R_3 = R_2X, \qquad (IV)$$

wherein
X is $-COOR_1$ or $-CH_2OH$, where R_1 is hydrogen or C_1-C_4 alkyl, wherein R_2 is a saturated hydrocarbon chain and R_3 is a saturated or unsaturated hydrocarbon chain and wherein R_2 and R_3 have a total of from 19 to 35 carbon atoms,
comprising the operation of reacting a compound of formula (V):

$$O = R_2\text{-}COOR_1,$$

wherein
R_1 is hydrogen or C_1-C_4 alkyl and
n is an integer from 6 to 12,
with a phosphorus ylide of formula (VI):

$$R_3P(Ar)_3,$$

wherein R_3 has the meaning defined above, under Wittig reac-

tion conditions.

17. A process according to claim 16, wherein R_3 is a hydrocarbon chain having from 8 to 22 carbon atoms, preferably from 10 to 20 carbon atoms including from 1 to 4 ethylenic and/or acetylenic unsaturations or their combinations.

18. A process according to claim 16 or 17, wherein R_2 is a linear or branched saturated hydrocarbon chain having from 4 to 15, preferably from 7 to 13, carbon atoms.

19. A process according to claim 16, characterized in that R_3 is a hydrocarbon chain which is linear or branched, including from 1 to 4 methyl branches, and which is optionally substituted by hydroxy.

20. A process according to claim 17, wherein R_3 is the hydrocarbon chain of a naturally occurring fatty acid.

21. A C_1-C_4 alkyl ester of polycosenoic acid, useful as an intermediate in the preparation of polycosanoic acid or polycosanol.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C51/347 C07C69/26 C07C67/343 C07C69/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOCELYN G. MILLAR: "Preparative Scale Synthesis of Isomerically Pure (10E,12E,14Z)- and (10E,12E,14E)-Hexadeca-10,12,14-trienals, Sex Hormone Components of Manduca Sexta" SYNTHESIS, no. 1, 2000, pages 113-118, XP002259681 page 115, right-hand column, line 7 - line 10; figure 3	1
A	the whole document	2-21
	See reaction 9+11 gives 12	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2003	17/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bedel, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 8529911 XP002259682 abstract & RAO B. V. S. K.: ORG. PREP. PROCED. INT., vol. 24, no. 1, 1992, pages 67-70,	1-21
A	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 8521326 XP002259683 abstract & VINCZER PETER: ORG. PREP. PROCED. INT., vol. 23, no. 4, 1991, pages 443-447,	1-21
X	EP 1 121 928 A (HAERTING S A) 8 August 2001 (2001-08-08) page 5; example 1	21

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/IB 03/02311

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1121928 A	08-08-2001	EP 1121928 A1	08-08-2001
		US 2002016314 A1	07-02-2002

Form PCT/ISA/210 (patent family annex) (July 1992)